Remarks

Rejection Under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-2, 6-15, 18, and 20-29 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicant respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Court of Appeals for the Federal Circuit (CAFC) described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a

claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

On page 7, lines 11-28, the specification discloses that the mechanism of the protein splicing process has been studied in great detail and **conserved** amino acids have been found at the intein and extein splicing points. In addition, the specification discloses a database (http://www.neb.com/neb/inteins.html) and a reference (Perler, F. B. *Nucleic Acids Research*, 1999, 27, 346-347), which discuss, **in detail**, intein landmarks, including conserved motifs, residues known to be involved in catalysis, and domain structure; the mechanism of protein splicing, including a detailed splicing pathway; a list of all known inteins and their properties with individual intein records containing intein name, prototype intein, extein gene, intein class, organism, domain of life, endonuclease activity or motifs, size, location in extein (position and

surrounding extein sequences), insertion site comments (extein motif, active site, etc.), and accession number. The Examiner is invited to discuss with the applicant the website and the reference to gain a full understanding of the amount of information that was known about inteins at the time the application was filed, should there be confusion or questions in this regard.

Although the claimed DNA constructs were not known, it would have been routine for one of ordinary skill in the art to modify or mutate one of the splice junction residues so that the exteins are excised but not ligated, since the **chemistry** of intein-mediated protein splicing, and the highly **conserved** splice junction residues were well characterized. For example, the disclosure teaches on page 9, lines 6-23 that mutation of serine 538 of the C-terminal extein junction in the *Pyroccoccus* species GB-DNA polymerase to alanine or glycine induces cleavage of the exteins but prevents subsequent extein ligation. Therefore, the serine to alanine/glycine mutation modifies the chemistry of the protein splicing mechanism in such a manner that cleavage, but not ligation, occurs. Because of the known chemistry and conserved amino acids, it would be routine for one of ordinary skill in the art to modify equivalent splice junction residues of other inteins, such as *Mycobacterium xenopi GyrA* protein or Saccharaomyces cerevisiae VMA intein in the same manner.

The courts have indicated that some experimentation is permitted as long as such experimentation is not undue. As stated in *MIT v. A.B. Fortia*, "The fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation". Applicant respectfully remind the Examiner that at the time the application was filed, high

throughput screening and methods to modify nucleotide sequences were routine in the art. Therefore, experimentation that may have been undue in the 1980's and 1990's, is not necessarily undue as of the year 2000. For example, scientists were only three years away from completing the Human Genome Project as of the filing date of this application.

Rejection Under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-2, 6-15, 18, and 20-29 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicant respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Court of Appeals for the Federal Circuit, in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 at 920, 69 USPQ 1886 (Fed. Cir. 2004), reviewed the standard of the written description requirement under 35 U.S.C. 112 and reiterated that the purpose of the written description requirement is separate from the enablement requirement, and "is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventors's contribution to the field of art as described in the patent specification,' *Reiffin v. Microsoft Corp.*, 214 F.3d 1342 at 1345 (Fed. Cir. 2000). "The 'written description' requirement serves a teaching function, as a '*quid pro quo*' in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time', citing to *Enzo Biochem, Inc. v. Gen-Probe Inc*, 323 F.3d 956 at 970 (Fed.

Cir. 2002). *University of Rochester* at 922. Citing again to *Enzo*, the court in *University of Rochester* at 920 stated "In *Enzo*, we explained that functional descriptions of genetic material can, in some cases, meet the written description requirement if those functional characteristics are 'coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.' 323 F.3d at 964 (quoting from the PTO's Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1 "Written Description" Requirement, 66 Fed. Reg. 1099, 1106)." (emphasis added). The Federal Circuit also stated in *University of Rochester* at 926 "We of course do not mean to suggest that the written description requirement can be satisfied only by providing a description of an actual reduction to practice."

The claims, as amended, are directed to DNA constructs with "one or more modified intein splicing units". Support for this amendment can be found, for example, on page 4, lines 10-28. The modified intein splicing unit is designed so that it can both catalyze excision of the exteins from the inteins as well as prevent ligation of the exteins. As stated above, on page 7, lines 18-21, the specification discloses a database (http://www.neb.com/neb/inteins.html) and a reference (Perler, F. B. *Nucleic Acids Research*, 1999, 27, 346-347), which discuss inteins in great detail, including essential regions of intein sequences that are required for an intein to function properly. The database of known inteins and their sequences is highly accessible to the public and may be considered a public depository. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002) *rev'd on rehearing*, 323 F3d 956 (2002). Furthermore, on pages 7-9, the specification sufficiently describes inteins and alludes to a number of other references, which

fully characterize inteins. As affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

The specification then describes the modification of intein splicing units that prevent ligation of cleaved exteins, and gives specific examples of inteins from *Pyroccoccus* species GB-DNA polymerase and *Mycobacterium xenopi* GyrA (page 9, lines 6-24). A "representative number of species" means that the species which are adequately described are representative of the entire genus. There may be a situation where one species adequately supports a genus. See, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27. As taught by the specification, the cited references and the intein database, which contains a list of all known inteins and their properties, intein structural motifs and the mechanism of the protein splicing process have been well characterized, and **highly conserved** amino acids have been found at intein and extein splicing points. The species disclosed by the Applicant are indeed representative of the entire genus of intein splicing units and one ordinary skill in the art would be able to modify equivalent residues of other intein splicing units to perform the claimed function.

The written description requirement does not require that one provide the description of everything that is known, so long as a reference is provided to direct one of ordinary skill in the art to what is required. This applicants have done. Applicants have also described specific examples, in complete detail, how they were made, tested, used and analyzed. One skilled in the

art could readily apply to the same modifications to the other known sequences. Accordingly, applicants have complied with the written description requirement.

Rejection Under 35 U.S.C. § 103

Claims 1, 6, 8, 10-11, 15, 20, 22, and 24-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Xu et al. *The EMBO Journal* 15(19): 5146-5153 (1996) ("Xu 1996") in view of Xu et al. *Cell* 75: 1371-1377 (1993) ("Xu 1993") and further in view of Inglebrecht et al. *The Plant Cell* 1: 671-680 (1989). Applicant respectfully traverse this rejection to the extent that it is applied to the claims as amended.

To establish a *prima facie* case of obviousness, the Examiner has the burden to prove that there is some suggestion or motivation to modify the reference or to combine reference teachings. *In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The MPEP explains that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combinations" (MPEP § 2143.01, quoting *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990)).

The Xu references describe protein splicing, but fail to teach a construct that contains a 3' termination sequence containing a polyadenylation signal following the last coding sequence. There is no suggestion of expressing the constructs in eukaryotic cells, and in fact, much of the work was performed in cell free transcription/translation systems. Inglebrecht does not teach a construct containing inteins, nor does it even mention protein splicing. Furthermore, the DNA

constructs taught by the Xu and Inglebrecht references have absolutely nothing in common. Xu teaches constructs made by inserting a Pyrococcus GB-DNA polymerase IVPS1 cassette into a plasmid carrying a fusion between *malE* and *D. immitus paramyosin Δ Sal* driven by an **isopropyl-β-D-thiogalactoside inducible** promoter. Inglebrecht teaches plasmids containing the coding sequence of neomycin phosphotransferase II fused to the **constitutive cauliflower mosaic virus 35S promoter** with and without the 3' end of the *octopine synthase* gene, the *Arabidopsis* 2S-1 gene, the *Arabidopsis* rbcS small subunit gene, the *Daucus carota* extension gene, or the *Antirrhinum majus* chalcone synthase gene. Because of the major differences in the constructs and the overall purpose of the studies, one of ordinary skill in the art would have no motivation to combine the Xu references with the Inglebrecht references.

Therefore, it is clear that the Examiner has not established a *prima facie* case of obviousness and has impermissibly combined the teachings of the prior art using the current application as a roadmap for how they should be combined.

"Because a court has the benefit of seeing the elements already combined in the patent claims when determining whether it would have been obvious to combine the elements from the prior art references, an inherent temptation exists to 'Monday-morning quarterback.' However, § 103 requires that the invention be obvious 'at the time the invention was made,' not after the invention is disclosed. Therefore, in deciding the legal question of obviousness, the court may not look to the patent claims as a guide for combining different elements or limitations of the prior art references to piece together the patent claims... . That is, the court must determine

whether the invention would have been obvious 'at the time the invention was made' without the benefit of **hindsight** now that the inventor has taught the claimed invention to the court." (See *In re Minton vs. National Association of Security Dealers, Inc. 226 F. Supp.2d 845, 873-74 (E.D. Tex. 2002), aff'd*, 336 F.3d 1373 (Fed. Cir. 2003)).

Allowance of claims 1, 6-15, 18 and 20-29 is respectfully solicited.

Respectfully submitted,

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